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Prognostic Role of Carbohydrate Antigen 19 to 9 in Predicting Survival of Patients With Pancreatic Cancer: A Meta-Analysis

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Abstract

This study evaluates the prognostic role of carbohydrate antigen 19 to 9 (CA19-9) in predicting survival of pancreatic cancer patients. Literature search was conducted in electronic databases (Google Scholar, Ovid, PubMed, and Science Direct) and study selection was based on precise eligibility criteria. Random-effects meta-analyses were performed to achieve overall estimates of median survival and hazard ratios (HRs) of survival with cutoff defined lower and higher CA19-9 levels before and after surgery or chemotherapy (CT)/radiotherapy (RT) and the changes in CA19-9 levels after any treatment. A total of 41 studies (6519 patients; 42% females; age 63.3 years [95% confidence interval [CI]: 62.2, 64.4]) were included. A pooled HR of 1.79 with a narrow 95% CI (1.58, 2.01) showed that higher CA19-9 levels or less decrease in CA19-9 levels after treatment predicted shorter survival. Median survival in patients with lower and higher preoperative CA19-9 levels was 23.2 months [95% CI: 17.2, 29.2] and 14.0 months [95% CI: 10.9, 17.2], respectively, whereas median survival with lower and higher postoperative CA19-9 levels was 25.0 months [95% CI: 21.9, 28.0] and 13.0 months [95% CI: 10.9, 15.0] respectively. Median survival with lower and higher pre-CT/RT CA19-9 levels was 11.9 months [95% CI: 10.2, 13.6] and 7.7 months [95% CI: 6.2, 9.2], respectively, whereas median survival with lower and higher post-CT/RT CA19-9 levels was 15.1 months [95% CI: 13.2, 17.0] and 10.7 months [95% CI: 7.3, 14.0] respectively. A decrease in CA19-9 levels after treatment was also associated with longer survival. Thus, both pretreatment and posttreatment CA19-9 levels or their changes after treatment have good prognostic value in determining the survival of pancreatic cancer patients.

Keywords

CA19-9, pancreatic cancer, prognosis, survival, predictor

Abbreviations

CA19-9, carbohydrate antigen 19 to 9; CI, confidence interval; HRs, hazard ratios.

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Introduction

Pancreatic cancer is the seventh leading cause of death.[1] Pancreatic exocrine adenocarcinoma accounts for approximately 85% of cases whereas the incidence of pancreatic endocrine tumors is relatively low.[2] In the United States of America, pancreatic cancer comprises 3% of all cancers and 7% of all cancer-related mortality but in China, it accounts for 19.5% of all cancers.[3,4] It is slightly more common in men than in women.[3] Worldwide, the estimated number of new cases of pancreatic cancer in 2018 was 458 918.[5] Later age, male gender, tobacco use, overweight or obesity, chronic pancreatitis, non-O blood group, diabetes mellitus, a diet high in fat and meat but low in vegetables and folate, occupational exposure to toxicants, family history, and genetic disorders (familial

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pancreatitis, Lynche syndrome, Peutz-Jeghers syndrome, etc) are important risk factors for pancreatic cancer.[3,6]

Pancreatic cancer is a slowly and silently progressing cancer that is usually diagnosed at a late stage.[7] Inherent resistance to chemotherapy and radiotherapy and its propensity for earlier metastasis makes pancreatic cancer difficult-to-treat cancer.[8] Five-years survival rate of patients with localized pancreatic cancer is 37%, but for patients with regional and distant metastasis, it is 12% and 3%, respectively.[3] At earlier stages, pancreatic cancer remains clinically silent. It is usually detected when the tumor invades surrounding areas or metastases to distant organs. Presenting symptoms which include abdominal or mid-back pain, obstructive jaundice, weight loss, asthenia, anorexia, nausea, duodenal obstruction, and gastrointestinal hemorrhage are usually dependent on the anatomical location of the tumor.[6,9] Diagnosis is mainly based on computed tomographic examinations which can also help in cancer staging and the prediction of surgical resection.[10] Serum levels of carbohydrate antigens 19 to 9 (CA19-9), CA125, CA242, carcinoembryonic antigen (CEA), and tumor-specific growth factors are important markers in the diagnosis of pancreatic cancer.[11]

Although pancreatic cancer is usually associated with a poor prognosis, several factors affect the prognosis. These include treatment, tumor location, stage, metastases, leucocyte count, hemoglobin, albumin, blood urea nitrogen, lactic dehydrogenase, alkaline phosphatase, aspartate aminotransferase, glutamic-pyruvic transaminase, CEA, CA19-9, CA125, and CA242.[11-13] The CA19-9, also called sialylated Lewis blood group antigen, is an important diagnostic and prognostic serum biomarker. Higher pretreatment CA19-9 levels are usually associated with a poor prognosis. Moreover, postoperative CA19-9 levels or the changes in CA19-9 levels after treatment can also provide prognostic information.[14,15] Several studies have reported survival outcomes of pancreatic cancer patients in association with CA19-9 levels but there is no systematic review of this area. We hypothesized that higher CA19-9 levels in pancreatic cancer patients predict shorter survival. The present study aimed to evaluate the prognostic role of CA19-9 in predicting the survival of pancreatic cancer patients by conducting a systematic review and performing a meta-analysis of survival outcomes in association with pretreatment and posttreatment CA19-9 levels or posttreatment changes in CA19-9 levels.

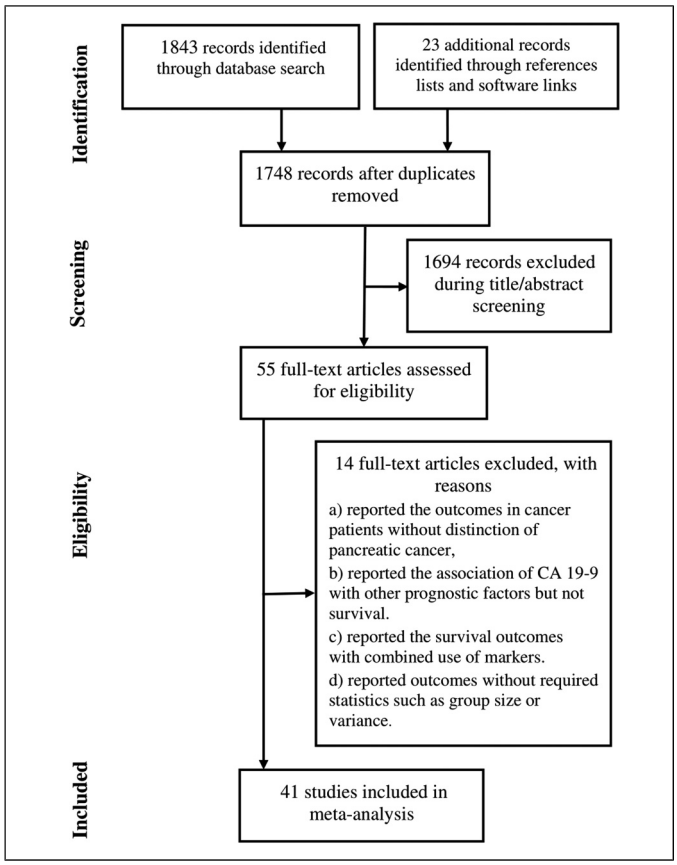

Figure 1. A flowchart of study screening and selection process.

Materials and Methods

This meta-analysis was performed by following Meta-Analysis of Observational Studies in Epidemiology guidelines.

Inclusion and Exclusion Criteria

Inclusion criteria were: A study (a) investigated the association between CA19-9 levels and survival of pancreatic cancer patients; (b) reported the hazard ratio (HR) depicting the associations between CA19-9 and survival; (c) reported the survival of patients with high and low CA19-9 levels before or after treatment (surgery and/or chemotherapy/radiotherapy); and (d) reported survival outcomes with the changes in CA19-9 levels after treatment. Exclusion criteria were: a study (a) reported the outcomes in cancer patients without distinction of pancreatic cancer; (b) reported the association of CA19-9 with other prognostic factors but not survival; (c) reported the survival outcomes with the combined use of markers; and (d) qualitative studies.

Literature Search

The literature search was conducted in Google Scholar, Ovid, PubMed, and Science Direct databases. Key terms used for literature search included pancreas, pancreatic, cancer, carcinoma, adenocarcinoma, prognosis, prognostic, predictor, carbohydrate antigen, CA19-9, sialylated Lewis blood group antigen, follow-up, survival, recurrence, and hazard. The literature search strategy is presented in Appendix S1. References lists of important research and review articles were also screened. Literature search encompassed original research articles published in English before September 2020.

Data Analyses

Demographic data, cancer stage, treatment, tumor size and location, performance status, pretreatment/posttreatment CA19-9

levels, CA19-9 cutoffs, survival outcome data, and HRs showing prognostic information were extracted from research articles of the included studies. Quality assessment of the included studies was performed with the Newcastle-Ottawa Scale for the Quality Assessment of Cohort Studies. Two reviewers extracted data and performed quality assessment independently and then outputs of both reviewers were unified. Interrater reliability was high. However, when these reviewers found difficulty in deciding, they sought the help of one or more co-researchers.

The HRs of survival between higher and lower CA19-9 levels or the changes in CA19-9 levels after treatment were pooled under the random-effects model to achieve overall and subgroup estimates. Median survival of patients with cutoff-defined lower and higher CA19-9 levels or the changes in CA19-9 levels after treatment were also pooled under the random-effects model by deriving variance from sample sizes. In these meta-analyses, the DerSimon-Liard method was used to achieve pooled estimates.

Subgroup analyses were performed for preoperative, pretherapy (chemotherapy; CT) and/or radiotherapy; RT), postoperative, post-CT/RT CA19-9 levels, or the changes in CA19-9 levels after any treatment. A sensitivity analysis was performed by excluding all studies with CA19-9 cutoff values other than the normal reference (37 U/mL). The I^2 index was used to estimate the proportion of observed variance reflecting true variance rather than sampling error. High I^2 values inform that true effect varies from study to study. All statistical analyses were performed with Stata software (version 12; Stata Corporation, College Station).

Results

Forty-one studies[13-52] were included in this meta-analysis (Figure 1). In these studies, 6519 patients with pancreatic cancer of which 42% (95% confidence interval [CI]: 40, 45) were females were evaluated. The average age of the patients was 63.3 years [95% CI: 62.2, 64.4]. Cancer was in the head of pancreas in 65% [95% CI: 57, 73] and in the body or tail in 31% [95% CI: 25, 39] of patients. Average pretreatment CA19-9 levels in these patients were 519 U/mL [95% CI: 362, 677]. Important characteristics of the included studies are presented in Table S1 (Supporting Information File). The quality of the included studies was good according to the Newcastle-Ottawa Scale (Table S2).

A pooled analysis of the HRs of survival between higher and lower CA19-9 levels yielded an overall HR of 1.79 [95% CI: 1.58, 2.01] which showed that higher CA19-9 levels were associated with shorter survival (Figure 2). Similar pooled HRs were observed for preoperative (1.70 [95% CI: 1.39, 2.00]), postoperative (2.07 [95% CI: 1.64, 2.49]), pretherapy (1.53 [95% CI: 1.20, 1.85]), and for the changes in CA19-9 levels after treatment (2.07 [1.31, 2.84]) subgroups. In these analyses, confidence intervals of pooled estimates were stringent and I^2 values ranged between 5% and 53%.

In the meta-analysis of studies that reported the survival with cutoff-defined lower and higher CA19-9 levels, median overall survival was 23.2 months [95% CI: 17.2, 29.2] with lower and 14.0 months [95% CI: 10.9, 17.2] with higher than cutoff preoperative CA19-9 levels. Median survival was 25.0 months [95% CI: 21.9, 28.0] with lower and 13.0 months [95% CI: 10.9, 15.0] with higher than cutoff postoperative CA19-9 levels. Median survival with lower and higher pre-CT/RT CA19-9 levels was 11.9 months [95% CI: 10.2 13.6] and 7.7 months [95% CI: 6.2, 9.2], respectively, whereas the median survival with lower and higher post-CT/RT CA19-9 levels was 15.1 months [95% CI: 13.2, 17.0] and 10.7 months [95% CI: 7.3, 14.0], respectively (Figure S1). In a sensitivity analysis with studies that used 37 U/mL cutoff for CA19-9 level to differentiate between lower and higher CA19-9 levels, the outcomes were not much different from those of the main meta-analysis (Figure S2).

In the meta-analysis of the changes in CA19-9 levels after treatment, it was found that the survival was longer with a cutoff defined decrease in CA19-9 levels after treatment. Survival was 11.1 months [95% CI: 10.0, 12.3] with >15% to 25% decrease, and 7.4 months [95% CI: 5.6, 9.2] with <15% to 25% decrease in CA19-9 levels after CT/RT. Similarly, survival was 11.1 months [95% CI: 9.6, 12.7] and 7.9 months [95% CI: 6.5, 9.4] with >50% and <50% decrease in CA19-9 levels after CT/RT, respectively (Figure 3).

Discussion

This meta-analysis has estimated a HR of 1.8 with narrow credibility limits to show that higher CA19-9 levels predict shorter survival in pancreatic cancer patients. Survival was considerably longer with cutoff-defined lower CA19-9 levels for both pretreatment and posttreatment samples. A cutoff-defined decrease in CA19-9 levels after treatment was also associated with longer survival. Different cutoff values for distinguishing lower and higher CA19-9 levels or their changes after treatment had generally similar survival outcomes.

Despite surgical resection even with no residual tumor, not all patients achieve a decrease in postoperative CA19-9 levels. It has been suggested that sustained elevations in CA19-9 levels may be due to micro-metastases such as hepatic micro-metastases which remain undetected at the time of surgery.[40] Patients with persistently higher CA19-9 levels are more likely to have metastases and perineural invasion.[8] The CA19-9 levels can be found elevated in benign conditions like pancreatitis which is frequently found in pancreatic cancer patients. Another source of CA19-9 is cholestasis in which it is excreted from the biliary epithelium.[28] Such conditions can also contribute to persistently higher CA19-9 levels.

Several differing cutoff values ranging from 35 to 1212 U/mL were used by the included studies to differentiate between lower and higher CA19-9 levels. In a sensitivity analysis of studies that used normal reference value (37 U/mL) as the cutoff to differentiate between higher and lower CA19-9

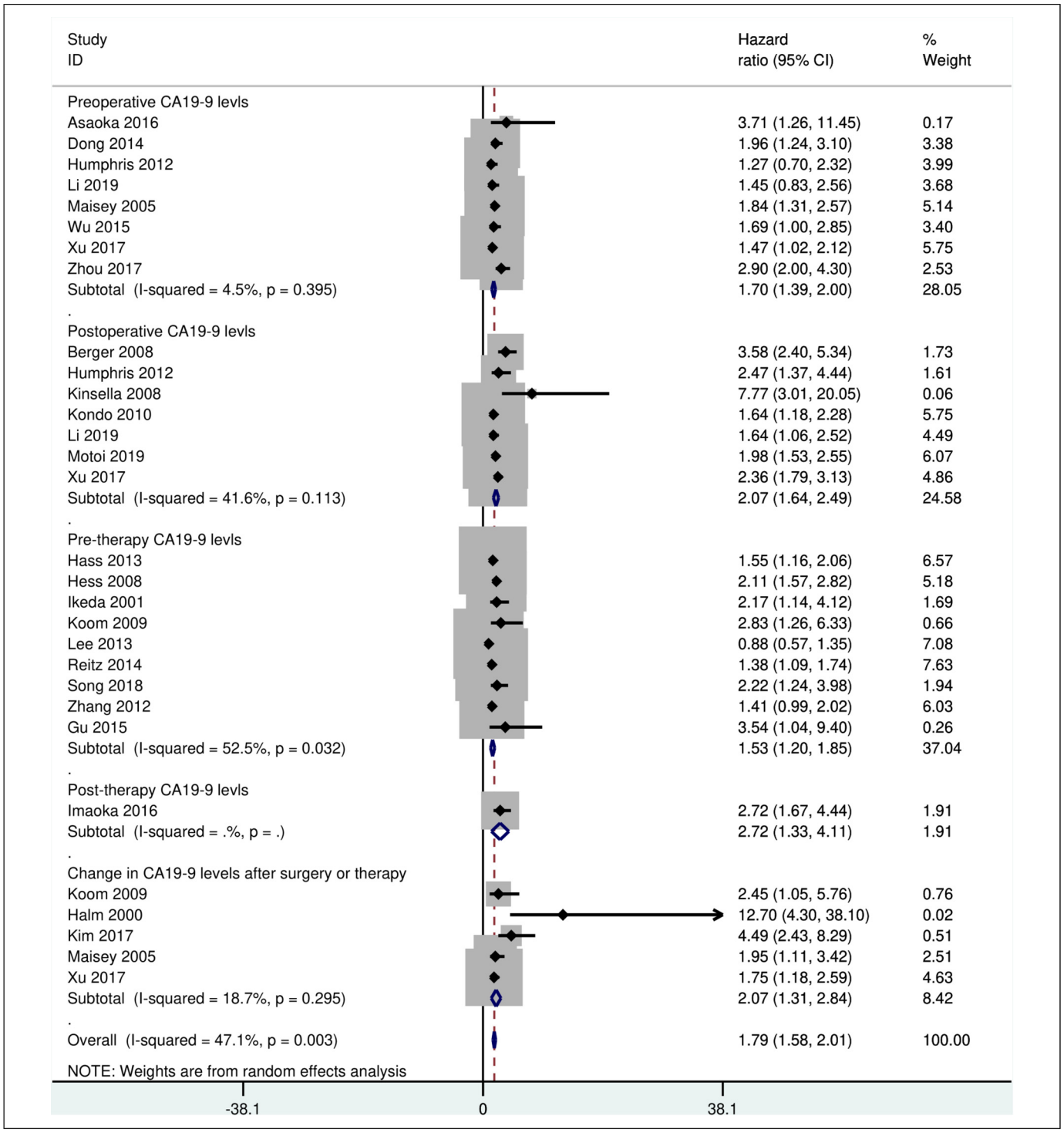

Figure 2. A forest graph showing the outcomes of meta-analysis of hazard ratios of survival between higher and lower preoperative, postoperative, pretreatment, posttreatment carbohydrate antigen 19 to 9 (CA19-9) levels, and the changes in CA19-9 levels after treatment.

levels, we could not find much difference in survival outcomes from those of the main meta-analysis. Individual studies that used multiple cutoffs also found similar outcomes. Kondo et al reported similar low versus high survival differences with the cutoffs of 37, 100, 200, and 500 U/mL. Koom et al[14] and Yoo et al[50] also found similar survival outcomes with different cutoffs. Kondo et al[15] and Koom et al[14] found postoperative CA19-9 levels to predict differential survival better than preoperative levels. However, Yoo et al[50] who also used several cutoffs, found both preoperative and postoperative CA19-9 levels to be equally useful to differentiate survival with lower and higher CA19-9 levels.

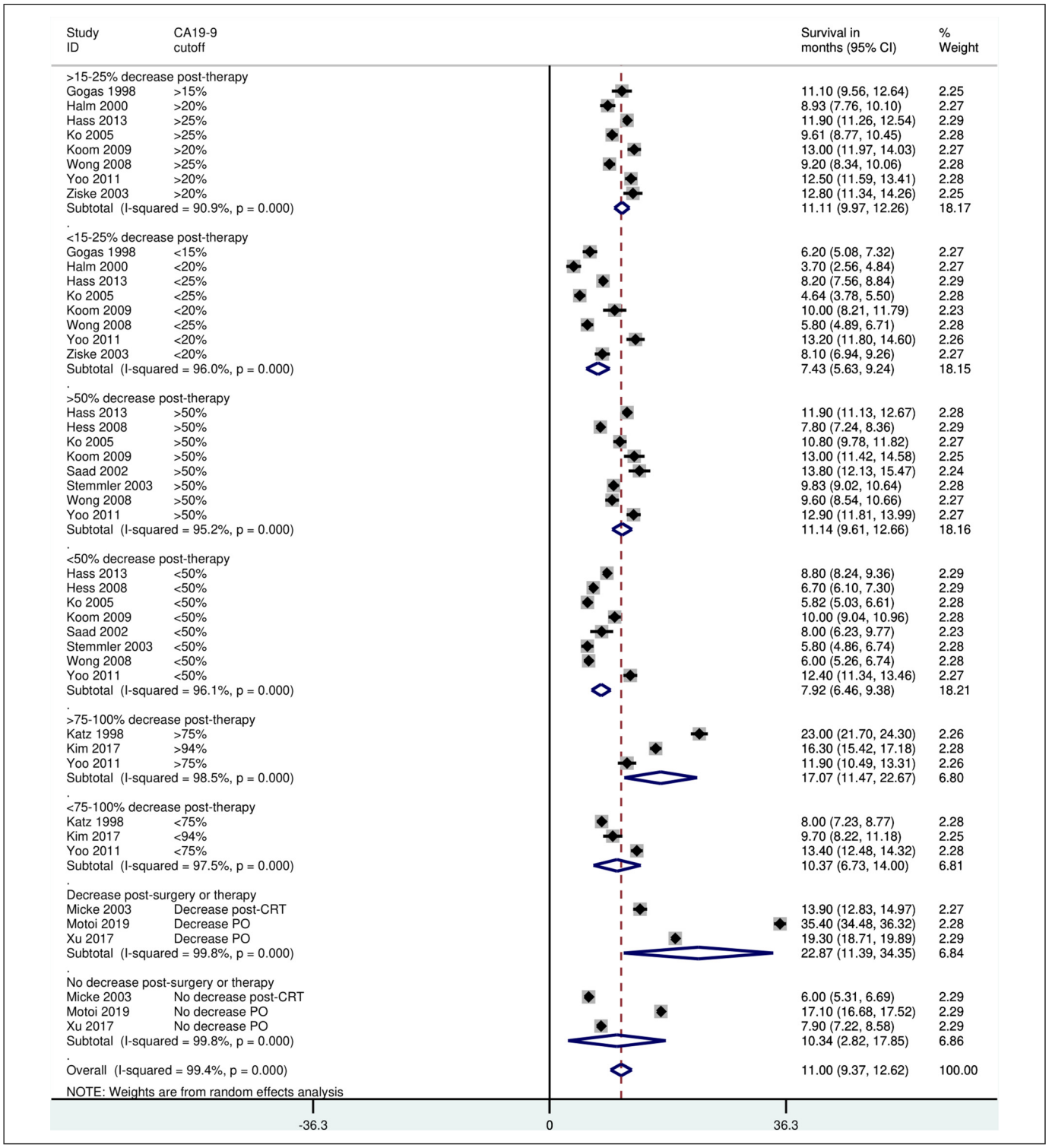

Figure 3. A forest graph showing the outcomes of meta-analysis of survival rates with higher and lower changes in CA19-9 levels after treatment with different cutoff values.
Abbreviations: CT, chemotherapy; CRT, chemoradiotherapy; PO, postoperative; CA19-9, carbohydrate antigen 19 to 9.

We have also observed a variation in the use of cutoff values by the individual studies in studying the survival outcomes with the changes in CA19-9 levels after treatment. These cutoffs ranged from 20% to 94% change in CA19-9 levels after treatment. However, differences in survival outcomes were generally similar with different cutoffs. It is suggested that a decrease from preoperative levels to postoperative levels or postoperative levels alone can help in the stratification of

patients for further treatments.[20] We have noticed that, in general, survival shortened with increasing cutoff values for both pretreatment and posttreatment CA19-9 levels in studies that used multiple cutoffs.[14,15,19,20,50] However, this trend was not clear for the decrease in CA19-9 levels after treatment. Ko et al found an increase in survival of 9.6, 10.8, and 12 months with 25%, 50%, and 75% decrease in posttherapy CA19-9 levels, respectively, but Koom et al[14] and Yoo et al[50] did not find such a dose–response change in the survival with multiple cutoffs of percent decrease in CA19-9 levels after treatment.[34]

It is usually accepted that patients with higher preoperative CA19-9 levels have a higher tumor burden and a higher risk of earlier death.[20] In patients with potentials for tumor resection, the preoperative CA19-9 levels predict tumor aggressiveness and disease burden which can help in disease staging as well as in decision-making for adjuvant treatment. Moreover, postoperative CA19-9 levels may also help in predicting the outcomes of adjuvant therapy.[23,28] A recently published meta-analysis has reported that a decrease or normalization of CA19-9 levels after neoadjuvant treatment was associated with better survival in pancreatic cancer patients.[53] A decrease in CA19-9 levels after treatment is also predictive of better prognosis in terms of patient's response to treatment, and remission of disease and consequently improved survival.[54]

Among the limitations of the present study, high I^2 values observed in the meta-analyses of survival with lower and higher CA19-9 levels are an important consideration. This high level of between-studies inconsistency in outcomes could be due to the use of several and wide-ranging cutoffs, clinical characteristics, and tumor stage. However, in the meta-analysis of HRs, the I^2 values were low to moderate which endorsed the outcomes of meta-analyses of survival with low and high CA19-9 levels.

In conclusion, this meta-analysis found that cutoff-defined lower pretreatment or posttreatment CA19-9 levels in pancreatic cancer patients predict longer survival. Moreover, cutoff-defined decreases in CA19-9 levels after treatment were also associated with better survival. Different cutoff values to differentiate between lower and higher CA19-9 levels or the changes in CA19-9 levels after treatment had generally similar survival outcomes.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Supplemental Material

Supplemental material for this article is available online.

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